electrical wave propagation on the cardiac tissue. The overall influence involves a combination of a decrease in the action potential amplitude and shortening of the action potential duration. This mechanism introduces both temporal and spatial dispersion of electrical excitability and heterogeneous conduction, leading to wave breaks and spontaneous arrhythmia when the mitochondrial energetics within the metabolic current sink zone is recovering. In summary, this study illustrates the mechanism by which "metabolic" sinks can contribute the formation of fatal reentrant arrhythmias and reveal a novel way that reentry may be triggered in tissues recovering from metabolic inhibition (e.g., ischemia-reperfusion). The findings underscore the importance of considering mitochondrial targets for developing new therapies for SCD in the context of cardiovascular disease.

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Mechanisms of Lethal Arrhythmia in Dilated Cardiomyopathy Model Mice

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Dilated cardiomyopathy (DCM) is associated with a high incidence of arrhythmias leading to sudden death, but little is known about the underlying basis for these arrhythmias. To understand the mechanistic basis for lethal arrhythmias in idiopathic DCM, the properties of the myocardium in terms of its arrhythmogenicity, were studied using a mouse model of inherited DCM with a deletion mutation in the cardiac troponin T gene (TNNT2) which decreases Ca^{2+} sensitivity of myofilaments. Ventricular myocardium and single myocytes were obtained from wild-type (WT) and DCM mice. Myocardial automaticity was evaluated by the frequency of spontaneous contractions and optically determined action potential and Ca^{2+} signals. Whole cell voltage clamp currents were measured from isolated myocytes. Expression of major K^+ channels and related proteins was determined by real-time PCR and Western blot analysis. In left ventricular myocardium of 2-month-old DCM mice prior to any sign of pulmonary edema, spontaneous activity frequently occurred and action potential duration was prolonged. Application of isoproterenol (Iso) to myocardium increased spontaneous activity more in DCM than WT. Correspondingly, Ca^{2+} waves and sparks were more marked in DCM in the presence of Iso. In DCM myocytes, transient outward current (I_{to}) and ultrarapid delayed rectifier K^+ current (I_{Kur}) were significantly reduced. In parallel, down-regulation of Kv4.2, Kv1.5 and KChIP2 was evident from real-time PCR and Western blot analyses. The reduction in these K^+ channels was less obvious at 1 month when death rate was lower. Inhibition of I_{Kur} by 4-aminopyridine partially mimicked the increase in automaticity in WT myocardium. Our results suggest that reduced contractile ability somehow causes an progressive decrease in K^+ channels and makes the heart susceptible to lethal arrhythmias before development of severe heart failure in DCM model mice.

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Accurate Prediction of Alternans in Cardiac Cells Using Stochastic Pacing and Transfer Function Analysis

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Alternans of action potential duration (APD) is a well-known arrhythmogenic mechanism. Studies based on eigenmode analysis demonstrated that alternans occurs when the eigenvalue λ_alt of the alternant eigenmode is < -1, providing an exact marker in contrast to the APD restitution slope. However, no method has been designed to estimate λ_alt experimentally.

We hypothesized that λ_alt can be obtained by pacing at cycle lengths (CLs) varying stochastically around a basic CL (BCL) and analyzing the transfer function between the time series of CLs and APDs. We expected that the pole of this transfer function closest to -1 corresponds to λ_alt.

We tested this hypothesis using a canine ventricular cell model in which alternans can be caused by unstable dynamics of membrane potential or of Ca2+ cycling. Control values of λ_alt were obtained analytically as a function of BCL. Stochastic pacing protocols were simulated for different BCLs and the poles and zeros of the corresponding transfer functions were estimated by fitting an autoregressive-moving-average (ARMA) model describing APD as a function of previous APDs and CLs.

In all model versions, the pole closest to -1 provided an accurate estimation of λ_alt and required the analysis of 30 successive APDs and CLs. During slow ramp decreases of BCL or slow changes of ion current conductances simulating drug application, small stochastic CL variations and ARMA model identification permitted to predict the onset of alternans by extrapolating the time course of the estimated λ_alt to -1.

In conclusion, stochastic pacing combined with ARMA model identification represents a novel approach to accurately evaluate the propensity to alternans. This method does not make any assumptions about the ionic mechanism of alternans and should be applicable experimentally for any type of myocardial cell.

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Models of Human Atrial Action Potential for Sinus Rhythm and Chronic Atrial Fibrillation

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The ionic mechanisms underlying remodeled atrial action potentials (AP) in chronic atrial fibrillation (cAF), particularly the role of intracellular Ca^{2+} dynamics, remain unclear. Our objectives were: 1) to develop a new human atrial cell model by implementing structural and ionic differences in atrial vs. ventricular cells from our recently published model of human ventricular myocytes with detailed Ca^{2+} handling; 2) to simulate APs in cAF by accounting for structural and electrical remodeling, and using recent data on altered Ca^{2+} homeostasis. Ionic currents in the ventricular model were modified based on experimental data in atrial vs. ventricular myocytes. Decreasing I_{K1} amplitude produced a ~10 mV depolarization shift in the atrial (vs. ventricular) resting membrane potential. $I_{to,fast}$ density was increased in the atrium, $I_{to,slow}$ was removed, and a formulation for the atrial-specific I_{Kur} was included. I_{NaCa} and I_{NaK} densities were reduced to account for lower protein expression in atrial vs. ventricular myocytes. The I_{NaK} diminution also caused $[Na]_i$ to rise. SERCA function was increased to reproduce faster $[Ca^{2+}]_i$ decline and relaxation in atrial cells. To simulate recent measured changes in cAF, we reduced I_{CaL}, I_{to} and I_{Kur} and SERCA, and increased I_{K1} and I_{NCX}. The baseline alterations to our ventricular model resulted in a typical type-3 human atrial AP morphology. Consistent with experimental findings, our sinus rhythm model showed reduced AP rate adaptation (i.e., shortening at increasing pacing frequencies) when partially blocking I_{CaL}, and suggested a crucial role of Ca^{2+} and Na^+ homeostasis in mediating this effect. This also explained impaired AP adaptation in cAF, with shorter APs. Our atrial model with detailed Ca^{2+} handling description provides a useful framework to study human cAF, as growing experimental evidence point to abnormal Ca^{2+} homeostasis as a key mediator in AF-pathophysiology.

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Sex and Regional Differences in Rabbit Right Ventricular L-Type Calcium Current Levels and Mathematical Modeling of Arrhythmia Vulnerability

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In adult rabbit left ventricular cardiac myocytes, sex and apex-base differences in cardiac L-type calcium current (ICa-L) levels were found to affect susceptibility to arrhythmogenic early afterdepolarizations (EADs). We have now investigated the role of ICa-L in EAD formation in right ventricular myocytes using the patch clamp technique to ascertain apex-base distribution and properties of the L-type calcium current in adult males and females. ICa-L density measured at 0mV was 84.6% higher in female (7.2 ± 0.83 pA/pF, n=8) than male base myocytes (3.9 ± 0.38, n=12, $p<0.001$). Regionally, the female right ventricle demonstrated 56.5% higher ICa-L density at the base (7.2 ± 0.83 pA/pF, n=8) than apex (4.56 ± 0.45 pA/pF, n=9, $p<0.02$). No gender differences in ICa-L density were seen in male-female apex myocytes. Additionally, we found no gender or regional differences in the voltage dependence of ICa-L activation and inactivation. Utilizing this data, we performed numerical simulations with a modified version of the Luo Rudy mathematical model of cardiac action potentials (APs). Under 50% suppression of the rapidly inactivating delayed rectifier potassium current to model Long QT Syndrome Type 2 (LQTS2), female base myocyte simulations exhibited longer APs and increased EAD vulnerability as compared to male base myocytes. The biophysical data and mathematical simulations together support the hypothesis that higher levels of ICa-L contribute to EAD genesis. Clinical studies show that recovery from beta-adrenergic stimulation is associated with increased likelihood of arrhythmia. Other studies have found that beta-adrenergic stimulation results in enhancement of ICa-L and slowly inactivating delayed rectifier potassium current (IKs). We hypothesize that IKs may recover from beta-adrenergic stimulation more rapidly than ICa-L, which could increase arrhythmia propensity. We are testing this hypothesis in model simulations of male and female base and apical myocytes.

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A Computational Model for the Effect that a *KCNQ1* Mutation Linked to Jervell and Lange-Nielson Syndrome has on Human Cardiac Action Potential Duration

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The most common type of genotype-positive Long QT syndrome (LQTS) is caused by mutations in the genes that underlie the slowly-activating delayed-rectifier K^+ current in the heart (I_{Ks}). *KCNQ1* and *KCNE1*, which encode the α- and β-subunit of I_{Ks}, respectively, are linked to autosomal dominant (Romano Ward Syndrome) and recessive (Jervell and Lange-Nielsen Syndrome or JLN) forms of LQTS. Two siblings diagnosed with JLN were found to be homozygous for the T322M-KCNQ1 missense mutation (Zhang *et al., BMC Med Genet* 2008). Heterologous expression of T322M-KCNQ1 with KCNE1